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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

09/285858

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
5741-01-CA		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/15693	29/07/1998	21/08/1997

International Patent Classification (IPC) or national classification and IPC
A61K9/14

Applicant
WARNER-LAMBERT COMPANY et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/02/1999	20. 08. 1999

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Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/15693

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-16 as originally filed

Claims, No.:

1-7 as originally filed

Drawings, sheets:

1/12-12/12 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4
	No:	Claims	1-3,5-7
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
D1: WO-A-9311749
D2: JP5004919 (Chemical Abstract 118:240956)
D3: WO-A-9532713 (Chemical Abstract 124:156003)
D4: US-A-5641516
D5: EP-A-740934
D6: EP-A-137198
D7: EP-A-552708
D8: EP-A-580860

2. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of Claims 1-3,5-7 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

The document D1 discloses solid dispersion of glitazone compounds with a water-soluble polymer (see D1, page 5, line 5 - page 6, line 17; page 7, line 8- page 8, line 3; pages 8-10, examples 1-3). Consequently, the subject-matter of claims 1,2,3,7 is not new over D1 (Article 33(2) PCT).

The documents D2 and D3 also relate to solid dispersions of troglitazone with water soluble polymers. Consequently, the subject-matter of claims 1,2,3,7 is not new over D2, and the subject-matter of claims 1,2,36 is not new over D2 (Article 33(2) PCT).

Lack of novelty of the following claims is further emphasized by the following documents, which all concern solid dispersion of "sparingly water-soluble" pharmaceutical agents in water-soluble polymers:
- lack of novelty of claims 1, 5-7 over D4 (see D4, col. 4, l. 47-52; col. 5, Table 1; col. 4,5 examples 1-7)
- lack of novelty of claims 1, 5-7 over D5 (see D5, col. 5, example 1; col. 6,7, examples 12, 19)
- lack of novelty of claims 1, 5,6 over D6 (see D6, p. 2, l. 3-15; p. 7, example 3)

- lack of novelty of claims 1;5;6 over D7 (see D7, p. 8, examples 3;5)
- lack of novelty of claim 1 over D8 (see D8, p. 7, example 4)

3. The documents D1, D2, D3, D4, D5, D6, D7 and D8 appear to be of particular relevance as far as inventive step is concerned (Article 33(3) PCT). These documents solve indeed the same problem, namely making a solid dispersion of "sparingly water soluble" particulate pharmaceutical agent in a water-soluble polymer, so that, as far as novel subject-matter is concerned, the present application does apparently not fulfill the requirements of Article 33(3) PCT over these prior art documents.
It seems in particular to be a normal design option to replace a known glitazone active compound by another in known processes and pharmaceutical forms, for the same effect. Consequently, the subject-matter of claim 4 does not seem to be inventive.

Therefore the present application does apparently not fulfill the requirements of Article 33(3) PCT

Re Item VII
Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D2, D3, D4, D5, D6, D7 and D8 is not mentioned in the description, nor are these documents identified therein.

2. The statement "incorporated herein by reference", on page 4 is obviously irrelevant and unnecessary, contrary to the requirements of Rule 9.1.iv PCT.

3. The statement page 7, lines 28-29 is obviously irrelevant and unnecessary, contrary to Rule 5(1)(a)(v) PCT.

Re Item VIII
Certain observations on the international application

1. According to the description of the present application, the term "a sparingly water-soluble particulate pharmaceutical agent" refers to pharmaceutical agents having a

solubility of 1 gram in 30 to 100 grams of water at 25°C, corresponding to the definition of the U.S. Pharmacopeia (see descrition, page 3, lines 27- 29). However, at least some compounds listed on page 4, lines 5-26 do have a different solubility property in water. One gram of salicylic acid is for instance soluble in 460 grams of water. Consequently, the term "a sparingly water-soluble particulate pharmaceutical agent" used in claim 1 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, and this term also implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.
Claim 1 does therefore not meet the requirements of Article 6 PCT.

2. The term "water soluble polymer" is referred in the description to compounds like tweens or lecithin, which are in fact not polymers (see the description, page 4, line 27- page 5, l. 11).
Consequently, this term used in claim 1 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, and this term also implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.
Claim 1 does therefore not meet the requirements of Article 6 PCT.

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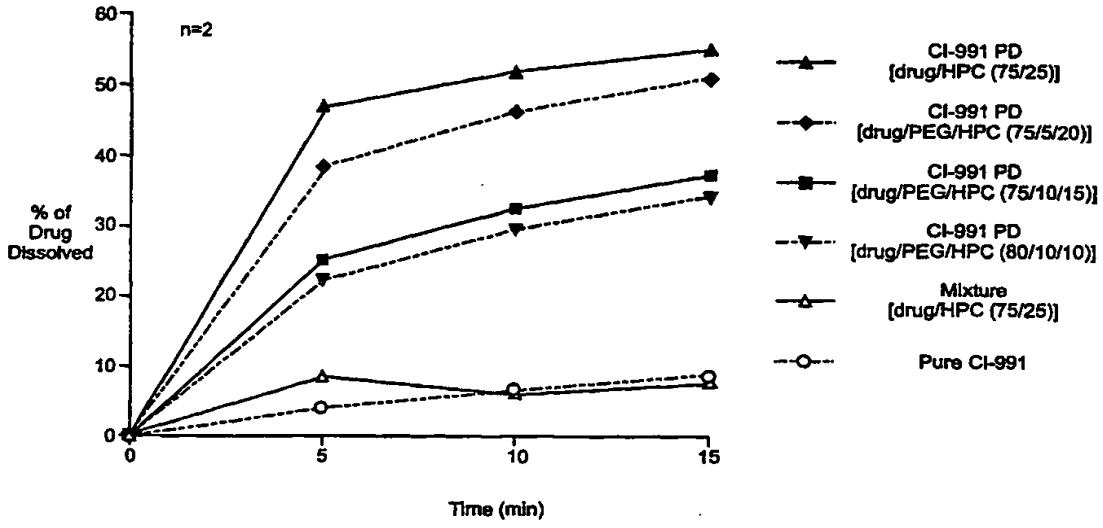
(54) Title: SOLID PHARMACEUTICAL DOSAGE FORMS IN FORM OF A PARTICULATE DISPERSION



(57) Abstract

Solid particulate dispersions of pharmaceutical agents in a matrix of a water-soluble polymer exhibiting good aqueous dissolution enhanced bioavailability. The method of the invention utilizes water-soluble polymers such as polyvinylpyrrolidone, hydroxypropyl cellulose or hydroxypropylmethyl cellulose as carriers. The invention provides for mixing or extracting the active ingredients in solid particulate form with the polymeric carrier at a temperature at which the polymer softens, or even melts, but the drug remains solid or crystalline. The drug particules thus become coated and produce a product that is matrix coated, i.e. a particulate dispersion.

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SOLID PHARMACEUTICAL DOSAGE FORMS IN FORM OF A PARTICULATE DISPERSION

FIELD OF THE INVENTION

This invention relates to orally bioavailable solid dosage forms of poorly water-soluble pharmaceutical agents.

BACKGROUND OF THE INVENTION

Many pharmaceutical agents are such highly complex chemical structures that they are insoluble or only sparingly soluble in water. This results in no or very low dissolution from conventional dosage forms designed for oral administration. Low dissolution rates results in no or very little bioavailability of the active chemical substance, thus making oral delivery ineffective therapeutically, and necessitating parenteral administration in order to achieve a beneficial therapeutic result. Drug products that are limited to parenteral delivery leads to increased costs of medical care, due to higher costs of manufacturing, more costly accessories required for delivery, and in many cases hospitalization of the patient to ensure proper dosing (e.g., sterile intravenous delivery).

Poorly water-soluble drugs that undergo dissolution rate-limited gastrointestinal absorption generally show increased bioavailability when the rate of dissolution is improved. To enhance the dissolution property and potentially the bioavailability of poorly water-soluble drugs, many strategies and methods have been proposed and used, which include particle size reduction, salt selection, formation of molecular complexes and solid dispersions, and the use of metastable polymorphic forms, co-solvents, and surface-active agents. Of these methods, the use of surface-active agents is mainly to improve the wettability of poorly water-soluble drugs, which eventually results in the enhancement of the rate of dissolution.

We have now discovered a method for producing solid particulate dosage forms of poorly water-soluble pharmaceutical agents, making them ideally suited

for oral administration, and providing enhanced dissolution rate in water and hence improved oral bioavailability. The method of this invention utilizes water-soluble polymers such as polyvinylpyrrolidone, hydroxypropyl cellulose, or hydroxypropyl methylcellulose as carriers. The use of these water-soluble carriers improves the wettability of the poorly water-soluble crystalline pharmaceutical agents, thus improving the rate of their dissolution following administration, and finally resulting in improved bioavailability and therapeutic result. The invention provides for mixing or extruding the active ingredients in solid particulate form with the polymeric carrier at a temperature at which the polymer softens, or even melts, but the drug remains solid or crystalline. The drug particles thus become coated and produce a product that is matrix coated, i.e., a particulate dispersion.

SUMMARY OF THE INVENTION

This invention provides solid dosage forms of sparingly water-soluble pharmaceutical agents. More particularly, the invention is a pharmaceutical composition in the form of a solid particulate dispersion of a particulate pharmaceutical ingredient dispersed throughout a matrix of a water-soluble polymer such as polyvinylpyrrolidone, hydroxypropyl cellulose, or hydroxypropyl methylcellulose.

In a preferred embodiment, the particulate pharmaceutical ingredient is dispersed in a water-soluble polymer in a weight ratio of about 10% to about 90% active ingredient to about 90% to about 10% polymer. A preferred formulation comprises about 20% to about 80% of active ingredient and about 80% to about 20% polymer. The most preferred composition comprises about 50% to about 80% solid active ingredient, and about 20% to 50% polymer or other excipients.

In another preferred embodiment, the pharmaceutical ingredient is dispersed in hydroxypropyl cellulose or hydroxypropyl methylcellulose. Especially preferred compositions comprise 40% to 80% by weight of active ingredient. The precise ratio of polymer to drug in the matrix is dictated by the particle size, and thus the surface area of the crystalline drug substance. Other conventional

excipients such as glycerin, propyleneglycol, Tween, stearic acid salts, polyvinyl pyrrolidones and the like can be added.

In an especially preferred embodiment, the sparingly soluble pharmaceutical agent utilized is selected from the class known as the glitazones. The glitazones are thiazolidinedione antidiabetic agents such as troglitazone, ciglitazone, pioglitazone, englitazone, and BRL 49653.

The most preferred composition of the invention is a solid dispersion of troglitazone in hydroxypropyl cellulose.

DETAILED DESCRIPTION OF THE INVENTION

The compositions provided by this invention are particulate dispersions of sparingly soluble pharmaceutical agents in a water-soluble polymer such as hydroxypropyl cellulose or hydroxypropyl methylcellulose.

Hydroxypropyl cellulose is also known as cellulose 2-hydroxypropyl ether, oxypropylated cellulose, and HPC. It is a non-ionic water-soluble ether of cellulose which exists as an off-white powder. While hydroxypropyl cellulose is soluble in many polar organic solvents, it readily precipitates from water at about 40°C. It is a thermoplastic material that has been utilized in the pharmaceutical field as an emulsifier, stabilizer, whipping aid, protective colloid, as well as a film former or thickener in foods.

Hydroxypropyl methylcellulose is cellulose 2-hydroxypropyl methyl ether or HPMC. It is a non-ionic water-soluble ether of methylcellulose, which is insoluble in hot water but dissolves slowly in cold water. It is more soluble than methylcellulose, and has been used extensively as an emulsifier, stabilizer, suspending agent, tablet excipient, and most notably as an ophthalmic lubricant. It is sold commercially as Ultra Tears, Tearisol, and Goniosol.

The compositions of this invention employ sparingly soluble pharmaceutical agents. The term "sparingly soluble pharmaceutical agent" means any solid or crystalline drug substance 1 gram of which will dissolve in from 30 to 100 grams of water at 25°C. Numerous drug substances are "sparingly soluble

pharmaceutical agents" as used herein, and can be employed to make the particulate dispersions of this invention. As noted above, a preferred group of such agents are the glitazones, especially troglitazone, also known as "CI-991". The glitazones are described more fully in United States Patent No. 5,478,852, which is incorporated herein by reference. Other agents that can be employed include antibiotics, such as cephalosporins and penicillins, the fluoroquinolinones such as clinafloxacin, the naphthyridinones such as CI-990, and the erythromycyl amine type compounds. Antihypertensive agents such as chlorothiazide and the ACE-inhibitors (quinapril, vasotec) can be formulated according to this invention. Anticancer agents such as methotrexate, suramin, and the vinca alkaloids can be employed.

Other pharmaceuticals which can be formulated as particulate dispersions include, but are not limited to acetohexamide, ajamaline, amylobarbitone, bendrofluazide, benzbromarone, benzonatate, benzylbenzoate, betamethazone, chloramphenicol, chlorpropamide, chlorthalidone, clofibrate, corticosteroids, diazepam, dicumerol, digitoxin, dihydroxypropyltheophylline, ergot alkaloids, ethotoin, frusemide, glutethimide, griseofulvin, hydrochlorothiazide, hydrocortisone, hydroflumethiazide, hydroquinone, hydroxyalkylxanthines, indomethacin, isoxsuprine hydrochloride, ketoprofen, khellin, meprobamate, nabilone, nicotainamide, nifedipine, nitrofurantoin, novalgin, nystatin, papaverine, paracetamol, phenylbutazone, phenobarbitone, prednisolone, prednisone, primadone, reserpine, romglizone, salicylic acid, spiranolactone, sulphabenzamide, sulphadiamadine, sulphamethoxydiazine, sulphamerazine, succinylsulphathiazole, sulphamethizole, sulphamethoxazole, sulphathiazole, sulphisoxazole, testosterone, tolazoline, tolbutamide, trifluoperazine, trimethaprim, and other water-insoluble drugs.

Any number of water-soluble polymers can be employed as a carrier for the particulate dispersion. All that is required is that the polymer be capable of softening or melting at a temperature that does not melt the solid drug substance, so that a matrix coating on the particulate drug substance can be formed. The polymer also must be sufficiently water soluble to allow dissolution of the particulate dispersion at a rate that provides the desired oral bioavailability and

resulting therapeutic benefit. Typical polymers to be employed include polyvinylpyrrolidone (PVP), polyethylene-oxides, pregelatinized starch, methylcellulose, hydroxyethylcellulose, polyvinyl alcohol, sodium alginate, sodium carboxymethylcellulose, lecithin, tweens, maltodextrin, poloxamer, sodium laurylsulfate, polyethylene glycol (PEG), vinyl acetate copolymer, Eudragit® acrylic polymers, E-100, and mixtures thereof. The carrier of choice obviously is dependent upon the drug to be dispersed but generally, the chosen carrier must be pharmacologically inert and chemically compatible with the drug in the solid state. They should not form highly bonded complexes with a strong association constant and most importantly should be freely water soluble with intrinsic rapid dissolution properties.

Another polymer of choice in most dispersions is PVP, which is a free flowing amorphous powder that is soluble in both water and organic solvents. It is hygroscopic in nature and compatible with a wide range of hydrophilic and hydrophobic resins. Another preferred carrier is a high molecular weight polyethylene glycol such as PEG 6000, which is a condensation polymer of ethylene glycol. Polyethylene glycols are generally a clear, colorless, odorless viscous liquid to waxy solid that is soluble or miscible with water.

The surprising and unexpected results of the present invention is the creation of a solid particulate pharmaceutical dispersion comprised of the aforementioned water-insoluble drugs and carriers without the need for using aqueous or organic solvents. In a further embodiment, the addition of a plasticizer/solubilizer during the mixing of the particulate drug and water-soluble polymer results in a chemical environment that readily lends itself to particulate dispersion formation.

Suitable plasticizers/solubilizers useful in the practice of the present invention include low molecular weight polyethylene glycols such as PEG 200, PEG 300, PEG 400, and PEG 600. Other suitable plasticizers include propylene glycol, glycerin, triacetin, and triethyl citrate. Optionally, a surfactant such as Tween 80 may be added to facilitate wettability within the formulation.

The water-insoluble drug of interest can first be milled to the desired particulate size, generally from about 1 micron to about 20 microns. It then is

blended with the polymeric carrier using any appropriate mixer or blender in a drug/carrier ratio of from about 1:9 to about 5:1, respectively, based upon a percentage weight basis. Preferably, the drug/carrier ratio will be approximately 3:1 to about 1:3, respectively. The blend is then transferred to a mixer, for example a low or high shear mixer or a fluid bed granulator, and additional excipients can be added, for example a plasticizer such as PEG 400, which can be dissolved in water with a surfactant such as Tween 80, if desired. Other suitable surfactants include Tweens 20 and 60, Span 20, Span 40, Pluronics, polyoxyethylene sorbitol esters, monoglycerides, polyoxyethylene acids, polyoxyethylene alcohols and mixtures thereof. Once all ingredients are sufficiently dissolved or suspended, the solution is sprayed onto the powder blend in the fluid bed granulator under specific conditions. The mixture can also be granulated in a low or high shear mixer, dried, and molded to produce the granulated product. The resultant granulation is transferred to a container and fed into a high intensity mixer such as a twin-screw extruder with at least one, and preferably more than one heating zones. The mixture is then extruded at appropriate temperatures depending on the heat stability of the drug, until a particulate dispersion is collected as an extrudate, which is then transferred to a drum for milling. The milled particulate pharmaceutical dispersion can then be ground into a powdery mass, and further blended with other excipients prior to encapsulation or being pressed into tablets. The final dosage form by may be optionally coated with a film such as hydroxypropyl methylcellulose, if desired.

In a preferred embodiment, particulate dispersions of the invention are prepared by melt extrusion of a pharmaceutical agent and about 10 to 90 weight percent of a polymer such as HPC. The melt extrusion is carried out by mixing the ingredients to uniformity at a temperature of about 50°C to about 200°C, the temperature being sufficiently high to melt or soften the polymer, but not so high to melt the drug particles. The melt or softened mixture is passed through a commercial twin-screw extruder. The resulting extrudate can be employed directly, or can be further processed, for example by milling or grinding to the desired consistency, and further admixed with conventional carriers such as starch, sucrose, talc and the like, and pressed into tablets or encapsulated. The final

dosage forms generally will contain about 1 mg to about 1000 mg of active ingredient, and more typically about 300 mg to about 800 mg.

BRIEF DESCRIPTION OF FIGURES

Figure 1 is the X-ray powder diffractogram of bulk troglitazone (CI-991).

Figure 2 is the X-ray powder diffractogram of the particulate dispersion of CI-991 in PEG-8000 and PVP in a weight ratio of 80:10:10.

Figure 3 is the X-ray powder diffractogram of the particulate dispersion of CI-991 in PEG-8000 and HPC in a weight ratio of 80:10:10.

Figure 4 is the X-ray powder diffractogram of the particulate dispersion of CI-991 in PEG-8000 and PVP in a weight ratio of 75:10:15.

Figure 5 is the X-ray powder diffractogram of the particulate dispersion of CI-991, PEG-8000, and HPC in the weight ratio of 75:10:15.

Figure 6 is the X-ray powder diffractogram of the particulate dispersion of CI-991, PEG-8000, and HPC in the weight ratio of 75:5:20.

Figure 7 is the X-ray powder diffractogram of the particulate dispersion of CI-991, and HPC in the weight ratio of 75:25.

Figure 8 is a comparison of dissolution profiles at pH 8 for various particulate dispersion formulations of CI-991.

Figure 9 is a comparison of dissolution profiles at pH 9 for various particulate dispersion formulations of CI-991.

Figure 10 is a comparison of dissolution profiles at pH 8 for two formulations of CI-991 in PVP.

Figure 11 is a comparison of dissolution profiles at pH 9 for two formulations of CI-991 in PVP.

Figure 12 is a comparison of dissolution profiles at pH 8 of various particulate dispersion formulations of CI-991.

The following detailed examples further illustrate the present invention. The examples are illustrative only and should not be construed to limit the invention in any respect.

EXAMPLE 1

Particulate Dispersion of Chlorothiazide

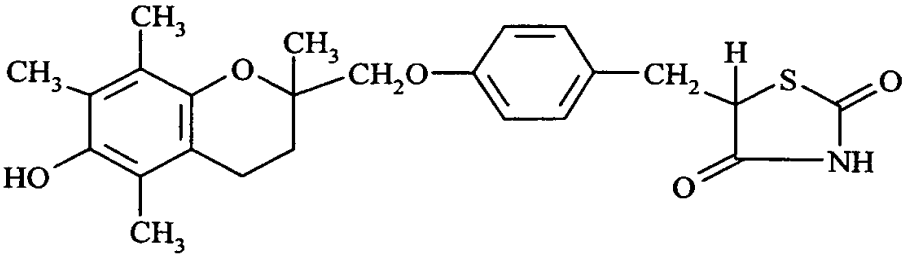
A mixture of 54 g of chlorothiazide and 6 g of hydroxypropyl cellulose were blended to uniformity at 24°C using a mortar and pestal. The mixture was transferred to a rotating mixing bowl and heated to 150°C, and tumbled at 50 rpm. The torque was maintained at 2000 meter-grams. The mixture congealed, and upon cooling to 24°C, was solid and uniform. The product was pulverized and milled, and pressed into tablets. Each tablet was a solid particulate formulation of chlorothiazide.

EXAMPLE 2

A mixture of 54 g of chlorothiazide and 6 g of hydroxypropyl methylcellulose were blended to uniformity at 24°C in a mortar and pestal. The mixture was added to a rotating mixing bowl and blended for 1 hour at 170°C at 50 rpm. The mixture was cooled, milled, and pressed into tablets which were solid particulate dispersions of chlorothiazide.

EXAMPLE 3

Troglitazone (CI-991), a new drug developed for the treatment of noninsulin-dependent diabetes, is a practically water-insoluble drug in gastrointestinal pH range of 1.0 to 7.5. To date, CI-991 has been prepared as a solid dispersion, in which the crystalline drug substance is converted to the amorphous form by hot melt extrusion methods, to enhance its rate of dissolution and oral bioavailability. In this study, CI-991 was used as a model drug to test whether the dissolution rate of poorly water-soluble drugs could be enhanced by the approach of forming a particulate dispersion in a matrix of a water-soluble polymer.



Troglitazone (CI-991)

Materials

CI-991 bulk drug (Lot XX020195) and the selected water-soluble excipients, including HPC, PVP K28-32, and PEG-8000, were all obtained from Centralized Raw Materials (Morris Plains, NJ). Chemicals used for preparing dissolution media, including disodium hydrogen phosphate (Na_2HPO_4), dipotassium hydrogen phosphate (K_2HPO_4), and 85% phosphoric acid (H_3PO_4), were obtained from J. T. Baker Co. (Phillisburg, NJ), whereas sodium lauryl sulfate (SLS) was obtained from Centralized Raw Materials.

Preparation of CI-991 Particulate Dispersions (PD)

CI-991 particulate dispersions were prepared by the mixing bowl method. The appropriate weights of CI-991 and excipients were placed in a screw-capped bottle and blended by a turbula mixer (Glen Mills Co., Maywood, NJ) for 15 minutes to give powder blends (or physical mixtures). About 65 grams of the powder blends were then mixed in a Brabender twin-screw mixing bowl (C. W. Brabender Instruments, South Hackensack, NJ) at 110°C or 130°C for 5 minutes. The resulting products (CI-991 PD) were collected, milled, and sieved. Samples having particle size between 80- and 100-mesh were used for dissolution study and other tests.

HPLC Assay of CI-991 Particulate Dispersions

The HPLC method used for the assay of CI-991 was adopted from RTD-0991-TAC-5 (pp. 5-12). HPLC analysis was conducted on a Hewlett-

Packard 1090 HPLC system equipped with a Hewlett-Packard 1050 absorbance detector and an Alltech Hypersil C18 column (4.6 × 100 mm, 3 μm). The mobile phase consisted of a 50:50 (% v/v) mixture of pH 3 (0.05 M) triethylamine buffer and acetonitrile. The flow rate was 1.5 mL/min, the UV detection wavelength was 225 nm, the injection volume was 20 μL, and the run time was 15 minutes. The retention time for the CI-991 peak was found to be around 5.6 minutes. Data acquisition and integration was performed with a Hewlett-Packard ChemStation software (Rev. A.02.00).

Characterization of Crystallinity

Crystallinity of the CI-991 particulate dispersions was characterized using X-ray powder diffractometry. X-ray powder diffraction patterns were recorded by using a Rigaku Geiger-Flex X-ray Diffractometer with Ni-filtered Cu-Kα radiation (λ = 1.5418 Å) over the interval 4-40°/2θ. In some cases, polarizing optical microscopy was used to confirm the results obtained from X-ray powder diffraction. The microscopic investigation was conducted in a Leitz Labolux 12 polarizing optical microscope equipped with a Polaroid camera.

Dissolution Studies

Preparation of Dissolution Media

<u>pH 8 (0.1 M) Phosphate Buffer Containing 0.5% (g/mL) SLS</u>

(0.1 M) Phosphate solution was prepared by dissolving a calculated amount of Na_2HPO_4 in USP water. The pH-value of the (0.1 M) phosphate solution was then adjusted to 8.0 ± 0.02 by 85% phosphoric acid to give a pH 8 (0.1 M) phosphate buffer. An appropriate amount of SLS was added and dissolved in the pH 8 (0.1 M) phosphate buffer to give the pH 8 (0.1 M) phosphate buffer containing 0.5% (g/mL) SLS.

<u>pH 9 (0.05 M) Phosphate Buffer</u>

(0.05 M) Phosphate solution was prepared by mixing 1:1 ratio of the aqueous solutions of (0.025 M) Na_2HPO_4 and (0.025 M) K_2HPO_4. The pH value

of the (0.05 M) phosphate solution was then adjusted to 9.0 ± 0.02 by 85% phosphoric acid to give the pH 9 (0.05 M) phosphate buffer.

Dissolution Testing

The dissolution studies were conducted in 900 mL of dissolution medium maintained at 37°C, using USP apparatus II (Distek 2100A dissolution system, North Brunswick, NJ) at 75 rpm of paddle speed. After dispersing a sample containing 100 mg of CI-991 into the dissolution medium, about 10 mL of solutions were periodically sampled and filtered by Gelman Nylon Acrodisc 0.45 μm filters to give clear filtrates (discard the first 2 mL filtrate). The extent of the drug dissolved in the dissolution medium was determined by UV spectrometry at $\lambda = 284$ nm. Interference by the excipients was not observed during analysis. Experiments were run in duplicate, and the results were averaged.

RESULTS AND DISCUSSION

Preparation and HPLC Assay of CI-991 Particulate Dispersions

Depending on sample sizes, particulate dispersion could be prepared by the mixing bowl or extrusion method. To minimize the quantity of CI-991 bulk drug utilized, CI-991 particulate dispersions were prepared using the mixing bowl method in this exploratory study. Since the melting range of CI-991 has been reported as 165°C to 175°C, the temperature applied to the mixing process should be lower than the melting temperature of CI-991 to prevent the drug from melting but should be high enough to soft or melt the water-soluble excipients used. By using this mixing bowl method, six CI-991 particulate dispersions, namely CI-991/PEG-8000/PVP (80:10:10), CI-991/PEG-8000/HPC (80:10:10), CI-991/PEG-8000/PVP (75:0:15), CI-991/PEG-8000/HPC (75:10:15), CI-991/PEG-8000/HPC (75:5:20), and CI-991/HPC (75:25) PD, were prepared at 110°C or 130°C [Table 1].

To investigate the chemical stability of CI-991 during the mixing process, the six CI-991 particulate dispersions were assayed using HPLC method. As presented in Table 1, the contents of drug measured from the six CI-991

particulate dispersions all agree well with those of the theoretical values, suggesting that CI-991 did not decompose significantly as the drug was mixed with PEG, HPC, and/or PVP at 110°C or 130°C.

TABLE 1. Preparation and HPLC Assay of Various CI-991/Polymer Particulate Dispersions (PD)

Sample ID	Formulation of CI-991 Particulate Dispersions	Precision Temperature °C	Percent of CI-991	
			Theoretical (%)	Assayed (%)
TD-0921096	CI-991/PEG-8000/PVP (80:10:10)	110	80	78.42 ± 0.33
TD-0931096	CI-991/PEG-8000/HPC (80:10:10)	110	80	78.41 ± 0.11
TD-0941096	CI-991/PEG-8000/PVP (75:10:15)	130	75	73.98 ± 0.12
TD-0951096	CI-991/PEG-8000/HPC (75:10:15)	130	75	73.79 ± 0.02
TD-0961096	CI-991/PEG-8000/HPC (75:5:20)	130	75	73.61 ± 0.05
TD-0971096	CI-991/HPC (75:25)	130	75	74.13 ± 0.24

X-ray Powder Diffraction Study

Since the mixing temperature (110 or 130°C) is well below the melting range of CI-991 (165-175°C), the drug is not expected to melt or convert to amorphous form during the formation of CI-991 particulate dispersion. The X-ray powder diffraction patterns of the CI-991 bulk drug and the six CI-991 particulates are shown in Figure 1 and in Figures 2-7, respectively. The crystalline properties of the bulk drug are characterized by several major diffraction peaks near 5.5, 11.8, 17.6, 19.6 and 23.7° (2θ), in the diffractogram [Figure 1]. For CI-991/PEG/PVP and CI-991/PEG/HPC (80:10:10) PD that were prepared at 110°C, their X-ray diffraction patterns [Figures 2-3] are almost identical to that of CI-991 bulk drug. Except a few weak diffraction peaks in the region of 8.5-0.5 2θ), most identifiable diffraction peaks of CI-991 are observed in the diffractograms of CI-991/PEG/PVP (75:10:15), CI-991/PEG/HPC (75:10:15), CI-991/PEG/HPC (75:5:20) and CI-991/HPC (75:25) PD [Figures 4-7], which were prepared at 130°C. Figures 1-7 also revealed that the CI-991 particulate dispersions, especially for those prepared at 130°C, exhibited broader diffraction peaks than the CI-991 bulk drug. These data may indicate that the crystalline bulk drug has been partially converted to the amorphous form and/or interacts with the

polymers used during the mixing process at elevated temperatures for the preparation of CI-991 particulate dispersions.

Dissolution Studies

The dissolution behaviors of the CI-991/polymer particulate dispersions were studied in two different dissolution media, namely pH 8 (0.1 M) phosphate buffer containing 0.5% SLS and pH 9 (0.05 M) phosphate buffer. The dissolution profiles of various CI-991/PEG-8000/HPC particulate dispersions in pH 8 (0.1 M) phosphate buffer containing 0.5% SLS and in pH 9 (0.05 M) phosphate buffer are shown in Figures 8 and 9, respectively. The dissolution profiles of the CI-991 bulk drug (or pure CI-991) and CI-991/HPC (75:25) physical mixture are also shown in Figures 8 and 9 for comparison.

It clearly indicates that all the four CI-991/HPC particulate dispersions exhibit a greater rate and extent of dissolution of CI-991 than the pure drug and physical mixture in these two dissolution media. The enhancement of dissolution rates of CI-991 would be mainly due to the increase of wettability of CI-991, since the drug has been coated with HPC and/or PEG-8000 (water-soluble polymers) during the formation of CI-991 particulate dispersion. In addition to the coating of water-soluble polymers, the rate of dissolution of CI-991 could be enhanced by the reduction of particle size since the drug might have been finely dispersed in the matrix of the polymers during the mixing process.

Of the four particulate dispersions studied, CI-991/HPC (75:25) PD exhibited the highest rate of dissolution. This is understandable because this particulate dispersion has the highest concentration of HPC, in which the resulting particulates would have the best wettability of the four CI-991/HPC particulate dispersions. The CI-991/HPC (75:25) PD yielded a 12-fold greater initial dissolution rate (computed over the first 5 minutes of dissolution) in pH (0.1 M) phosphate buffer containing 0.5% SLS than the pure CI-991 (Table 2 and Figure 8). In pH 9 (0.05 M) phosphate buffer, CI-991/HPC (75:25) PD also yielded a much greater initial dissolution rate than the pure CI-991 (Table 2 and Figure 9). After 15 minutes, this particulate dispersion produced a 7-fold greater dissolution rate in pH 8 (0.1 M) phosphate buffer containing 0.5% SLS and a

20-fold greater dissolution rate in pH 9 (0.05 M) phosphate buffer than the pure drug.

The dissolution profiles of CI-991/PEG-8000/PVP (80:10:10) and (75:10:15) PD in pH 8 (0.1 M) phosphate buffer containing 0.5% SLS and in pH 9 (0.05 M) phosphate buffer are shown in Figures 10 and 11, respectively. As with the CI-991/PEG-8000/HPC particulate dispersions, these two CI-991/PEG/PVP PD exhibited faster drug releasing profiles than the pure CI-991. Again, CI-991/PEG/PVP PD with higher concentration of PVP resulted in faster release of drug from the particulate dispersions (Figures 10 and 11). These dissolution studies also show that CI-991/PEG/HPC (80:10:10) and (75:10:15) PD have higher dissolution rates than the corresponding CI-991/PEG/PVP PD, especially in pH 8 (0.1 M) phosphate buffer containing 0.5% SLS (Figure 12). These data obtained may indicate that HPC is a better water-soluble polymer than PVP to enhance the rate of dissolution of drug for CI-991 particulate dispersion. The reason for these differences is not clear yet; however, it may be due to the different physical and chemical properties between HPC and PVP, such as glass transition temperature (T_g), rheological behavior at elevated temperatures, and/or drug-polymer interactions. Nevertheless, this study clearly demonstrated that the rate of dissolution of a poorly water-soluble drugs, CI-991, can be enhanced by the formation of particulate dispersion, in which the drug was coated with (or finely dispersed in) the water-soluble excipients, such as HPC and PVP, at high drug loading.

TABLE 2. Dissolution of Various CI-991/Polymer Particulate Dispersions (PD), Pure CI-991, and CI-991/HPC (75:25) Physical Mixture in Two Different Dissolution Media

Sample ID	Formulation	Percent of CI-991 Dissolved in Solution		
		at 5 min	at 10 min	at 15 min
A. In pH 8 (0.1 M) Phosphate Buffer Containing 0.5% SLS				
TD-0921096	CI-991/PEG-8000/PVP (80:10:10) PD	9.5 ± 0.3%	10.3 ± 0.5%	12.7 ± 0.6%
TD-0931096	CI-991/PEG-8000/PVP (80:10:10) PD	21.8 ± 0.5%	29.2 ± 0.1%	34.2 ± 0.1%
TD-0941096	CI-991/PEG-8000/PVP (75:10:15) PD	15.5 ± 2.9%	14.2 ± 0.4%	16.7 ± 0.5%
TD-0951096	CI-991/PEG-8000/HPC (75:10:15) PD	24.9 ± 0.1%	32.2 ± 0.2%	36.9 ± 0.2%
TD-0961096	CI-991/PEG-8000/HPC (75:5:20) PD	38.2 ± 1.9%	46.2 ± 0.5%	50.7 ± 0.5%
TD-0971096	CI-991/PEG-8000/HPC (75:25) PD	46.8 ± 3.3%	51.7 ± 1.6%	54.9 ± 1.4%
Lot XX020195	CI-991 Pure Drug	3.9 ± 0.1%	6.3 ± 0.1%	8.2 ± 0.1%
TD-0971096	CI-991/HPC (75:25) Physical Mixture	8.3 ± 1.8%	6.0 ± 0.1%	7.7 ± 0.1%
B. In pH 9 (0.05 M) Phosphate Buffer				
TD-0921096	CI-991/PEG-8000/PVP (80:10:10) PD	6.4 ± 0.3%	4.0 ± 0.4%	4.7 ± 0.4%
TD-0931096	CI-991/PEG-8000/HPC (80:10:10) PD	4.9 ± 0.4%	7.2 ± 0.1%	8.4 ± 0.1%
TD-0941096	CI-991/PEG-8000/PVP (75:10:15) PD	8.6 ± 0.1%	12.6 ± 0.3%	14.6 ± 0.2%
TD-0951096	CI-991/PEG-8000/HPC (75:10:15) PD	11.9 ± 1.6%	11.9 ± 0.1%	12.5 ± 0.4%
TD-0961096	CI-991/PEG-8000/HPC (75:5:20) PD	14.9 ± 0.9%	15.4 ± 0.6%	16.5 ± 0.2%
TD-0971096	CI-991/PEG-8000/HPC (75:25) PD	24.5 ± 0.4%	24.6 ± 0.3%	24.7 ± 0.3%
Lot XX020195	CI-991 Pure Drug	0.5 ± 0.1%	0.4 ± 0.1%	1.2 ± 0.2%
TD-0971096	CI-991/HPC (75:25) Physical Mixture	0.8 ± 0.1%	1.1 ± 0.1%	1.3 ± 0.1%

CONCLUSION

Six CI-991/polymer particulate dispersions (PD), namely CI-991/PEG-8000/PVP (80:10:10), CI-991/PEG-8000/HPC (80:10:10), CI-991/PEG-8000/PVP (75:10:15), CI-991/PEG-8000/HPC (75:10:15), CI-991/PEG-8000/HPC (75:5:20) and CI-991/HPC (75:25) PD, were prepared by the mixing bowl method at 110°C or 130°C. HPLC assay revealed that the drug contents of these particulate dispersions are almost identical to those of theoretical values, suggesting that CI-991 did not undergo significant decomposition during the mixing process at 110°C or 130°C. X-ray powder diffraction studies suggested that the drug substance in CI-991 particulate dispersions are mostly existed in the crystalline state. The six CI-991 particulate dispersions all exhibited faster drug releasing

profiles than the pure CI-991 and CI-991/HPC (75:25) physical mixture in pH 8 (0.1 M) phosphate buffer containing 0.5% (g/mL) SLS and in pH 9 (0.05 M) phosphate buffer. The enhancement of dissolution rate of drug could be mainly due to the increase of wettability and/or the reduction of particle size of CI-991 as the drug was coated with the highly water-soluble polymers such as HPC and PVP during the extrusion process. It is found that HPC appears to be a better water-soluble polymer than PVP to enhance the rate of dissolution of CI-991 from particulate dispersion. This study demonstrated that the rate of dissolution of high dose poorly water-soluble drugs such as CI-991 could be enhanced by improving the wettability of the drugs due to the formation of particulate dispersions.

CLAIMS

What is claimed is:

1. A solid particulate pharmaceutical dosage form suitable for oral delivery comprising a sparingly water-soluble particulate pharmaceutical agent dispersed throughout a matrix comprised of a water-soluble polymer.

2. A dosage form of Claim 1 wherein the pharmaceutical agent is a glitazone.

3. A dosage form of Claim 2 wherein the glitazone is troglitazone.

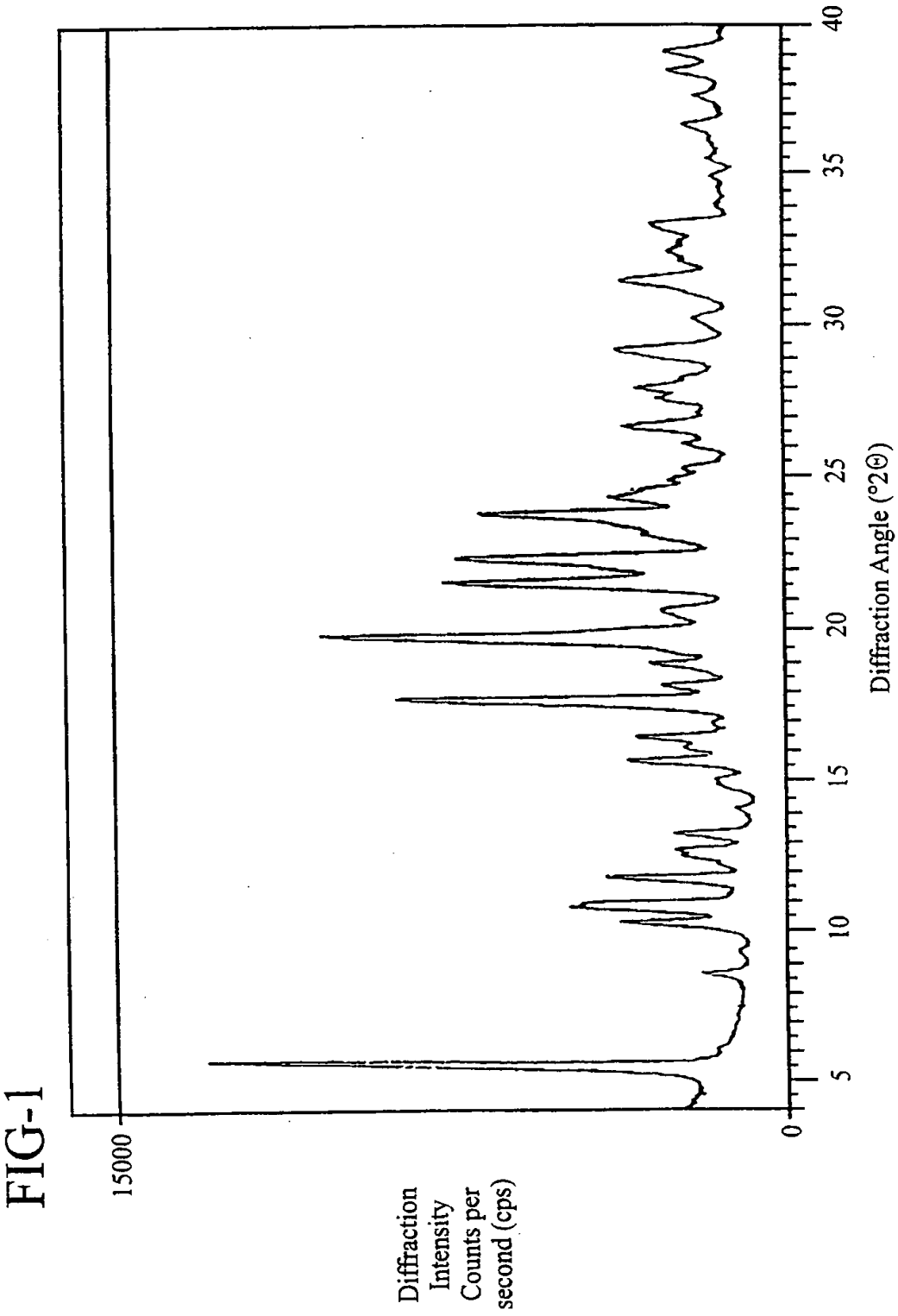
4. A dosage form of Claim 2 wherein the glitazone is BRL 49653.

5. A dosage form of Claim 1 wherein the polymer is hydroxypropyl cellulose.

6. A dosage form of Claim 1 wherein the polymer is hydroxypropyl methylcellulose.

7. A dosage form of Claim 1 wherein the polymer is polyvinylpyrrolidone.

FIG-1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20
25
30
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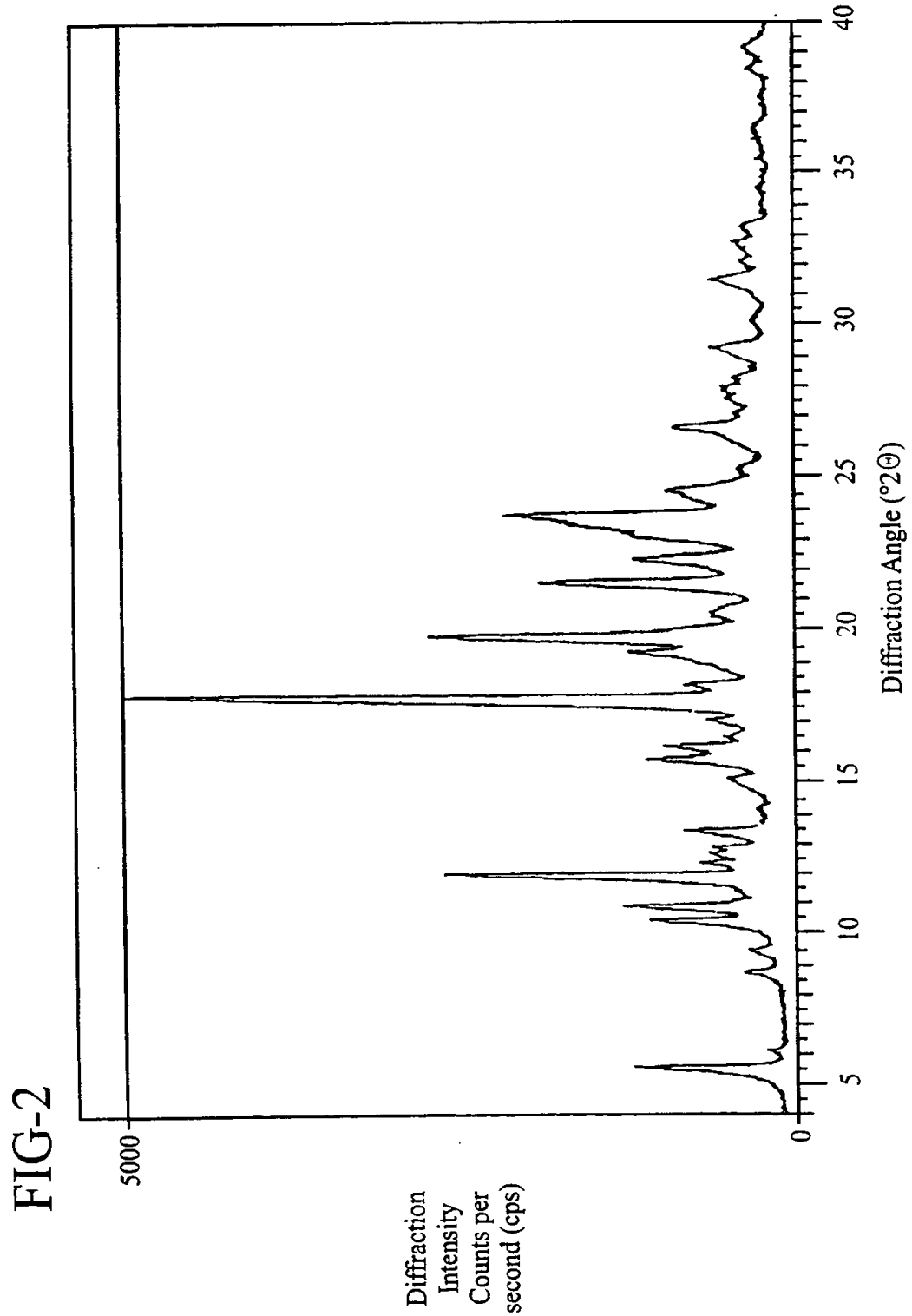
Diffraction Angle (°2Θ)

FIG-2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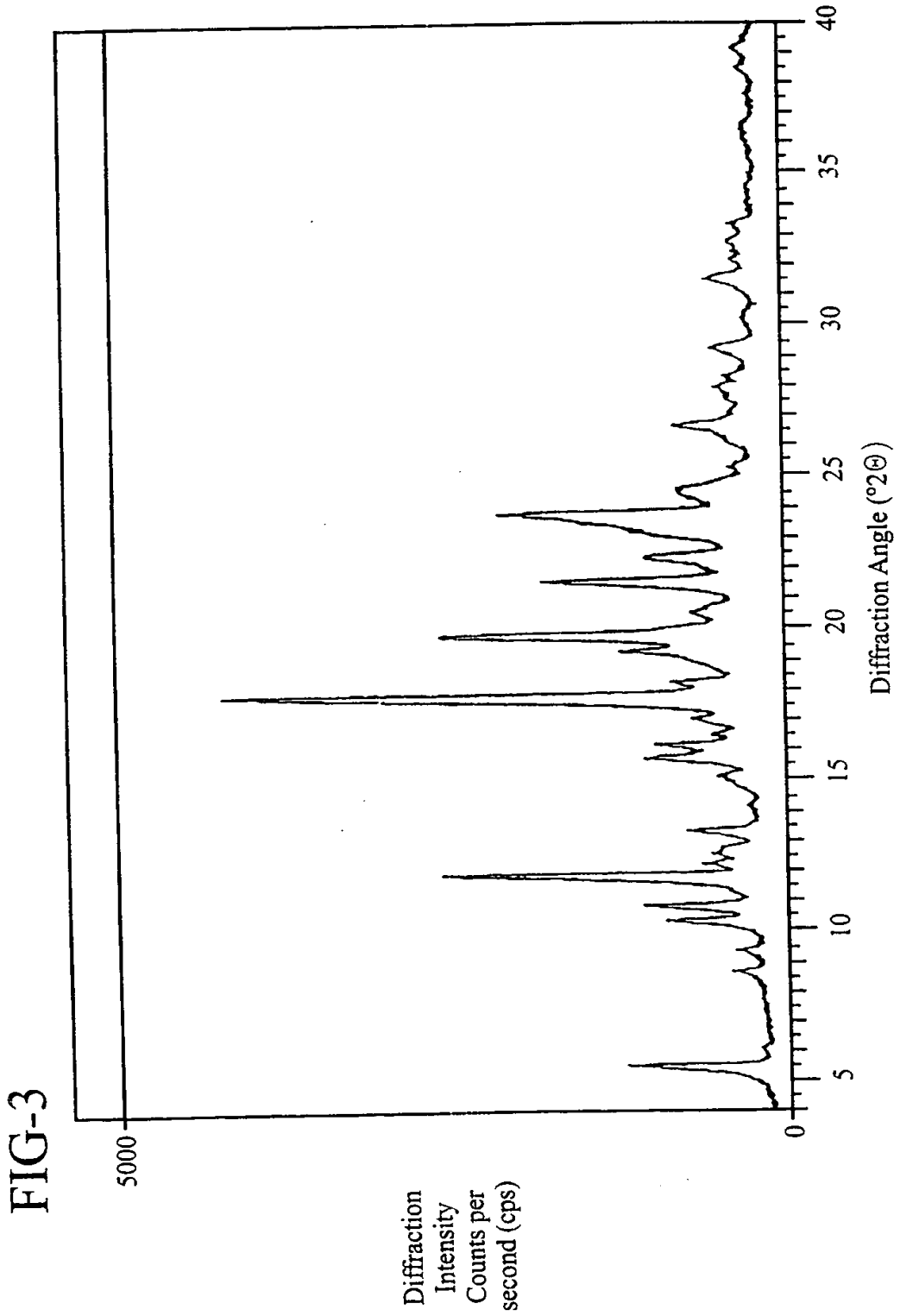
Diffraction Angle (°2Θ)

FIG-3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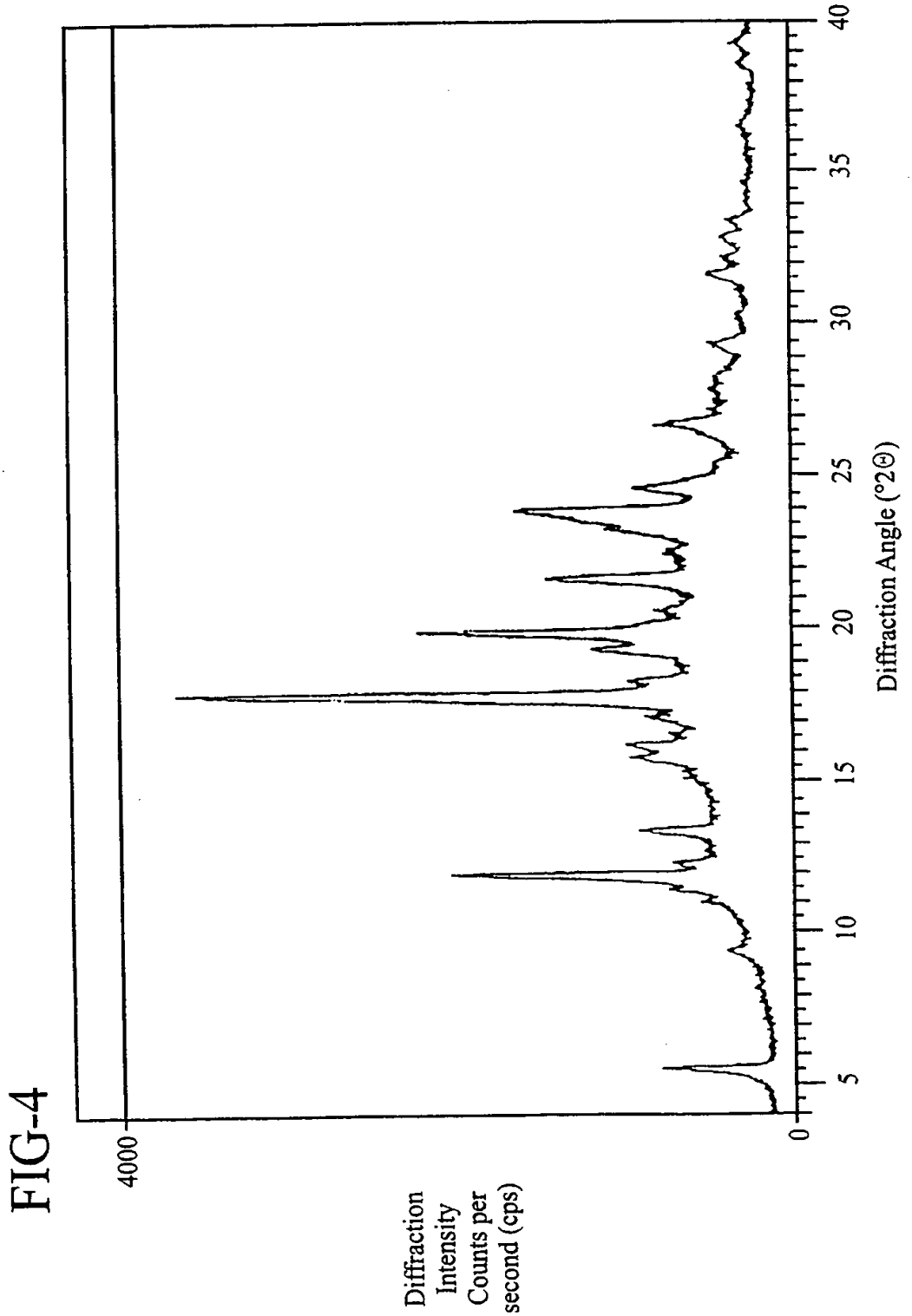
40
Diffraction Angle (°2Θ)

FIG-4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Diffraction Intensity Counts per second (cps)
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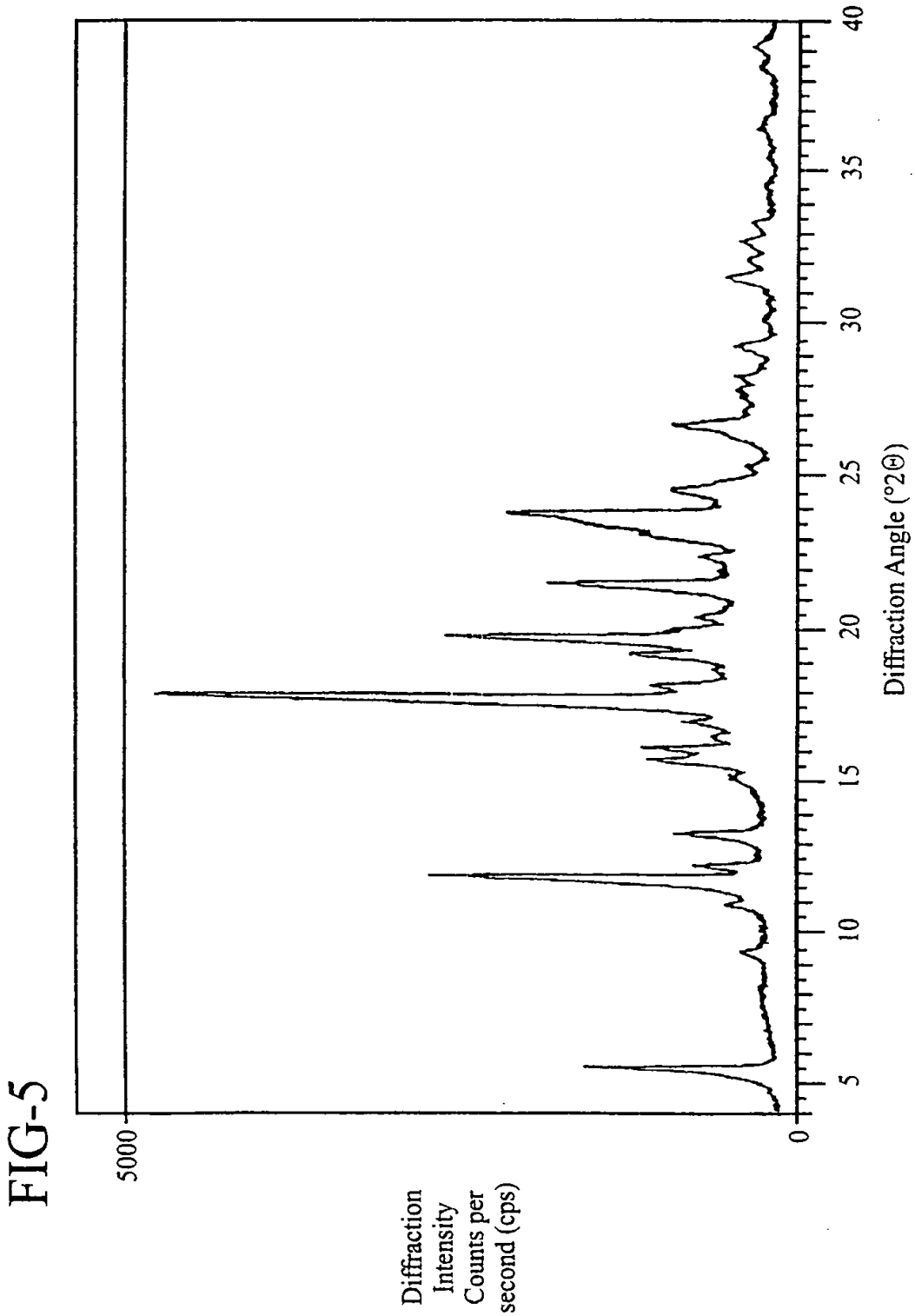
Diffraction Angle (°2Θ)

FIG-5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Diffraction Intensity Counts per second (cps)
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15
20
25
30
35
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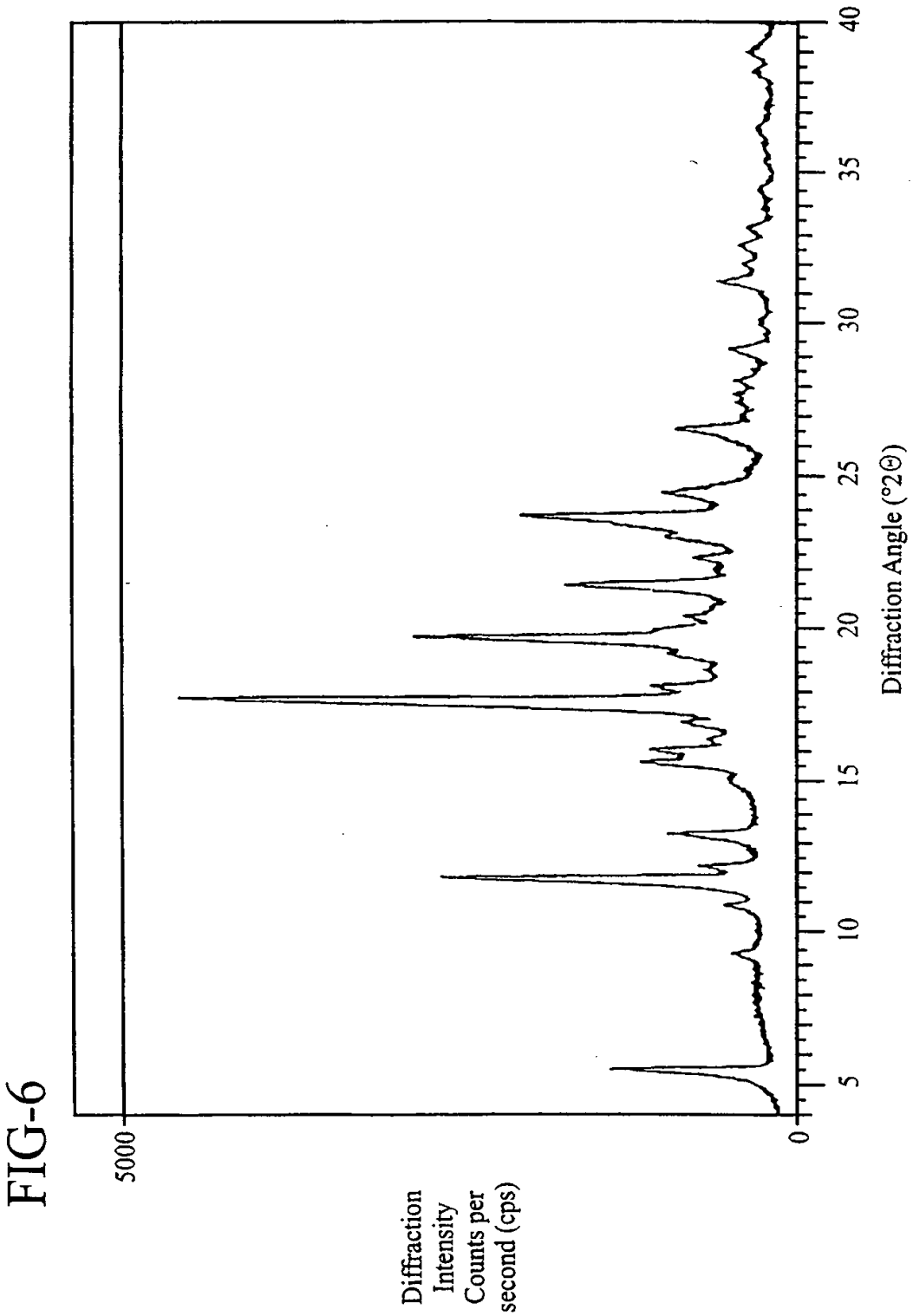
Diffraction Angle (°2Θ)

FIG-6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20
25
30
35
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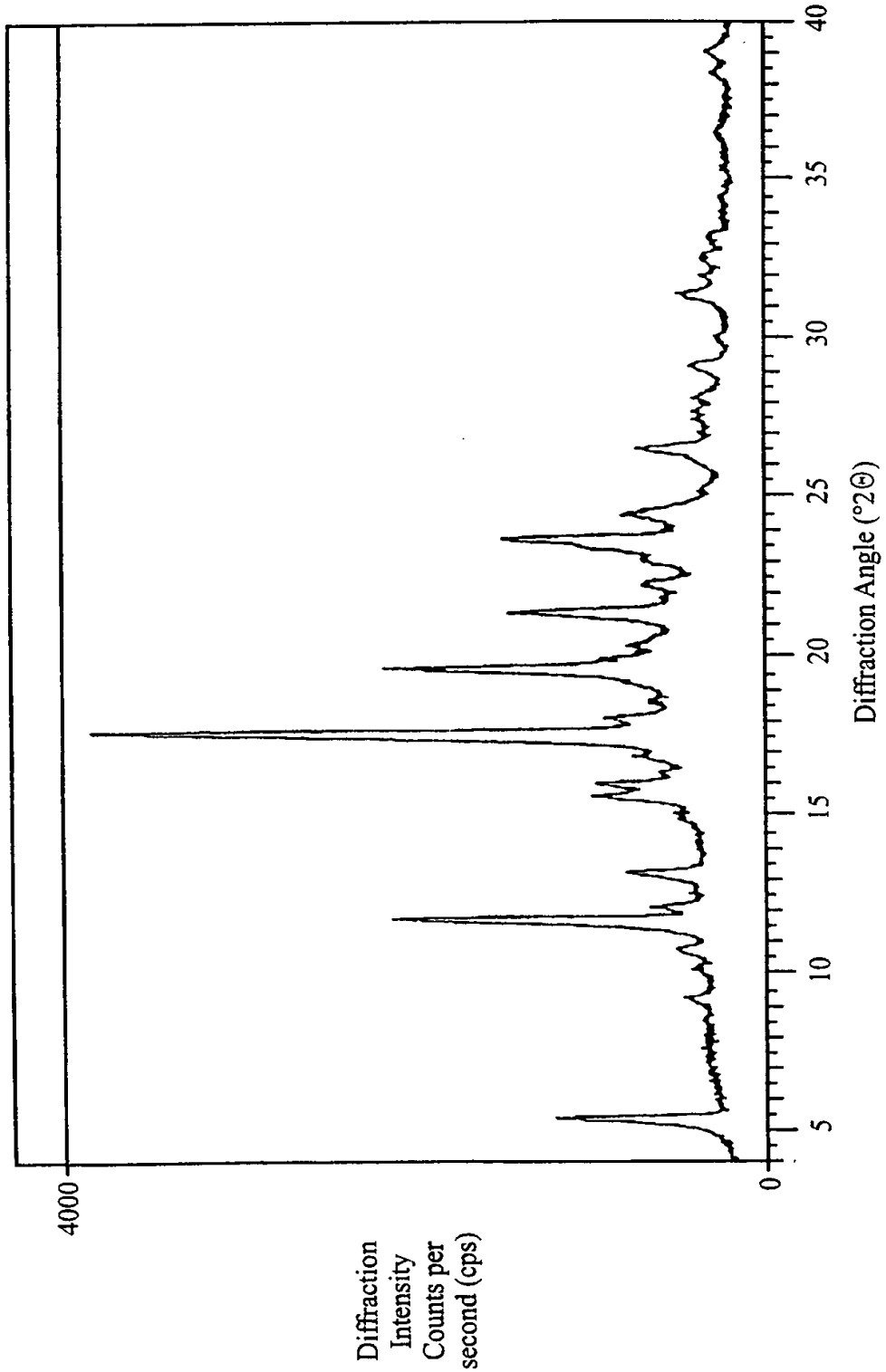
Diffraction Angle (°2Θ)

FIG-7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25
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35
40
Diffraction Angle (°2Θ)

FIG-8

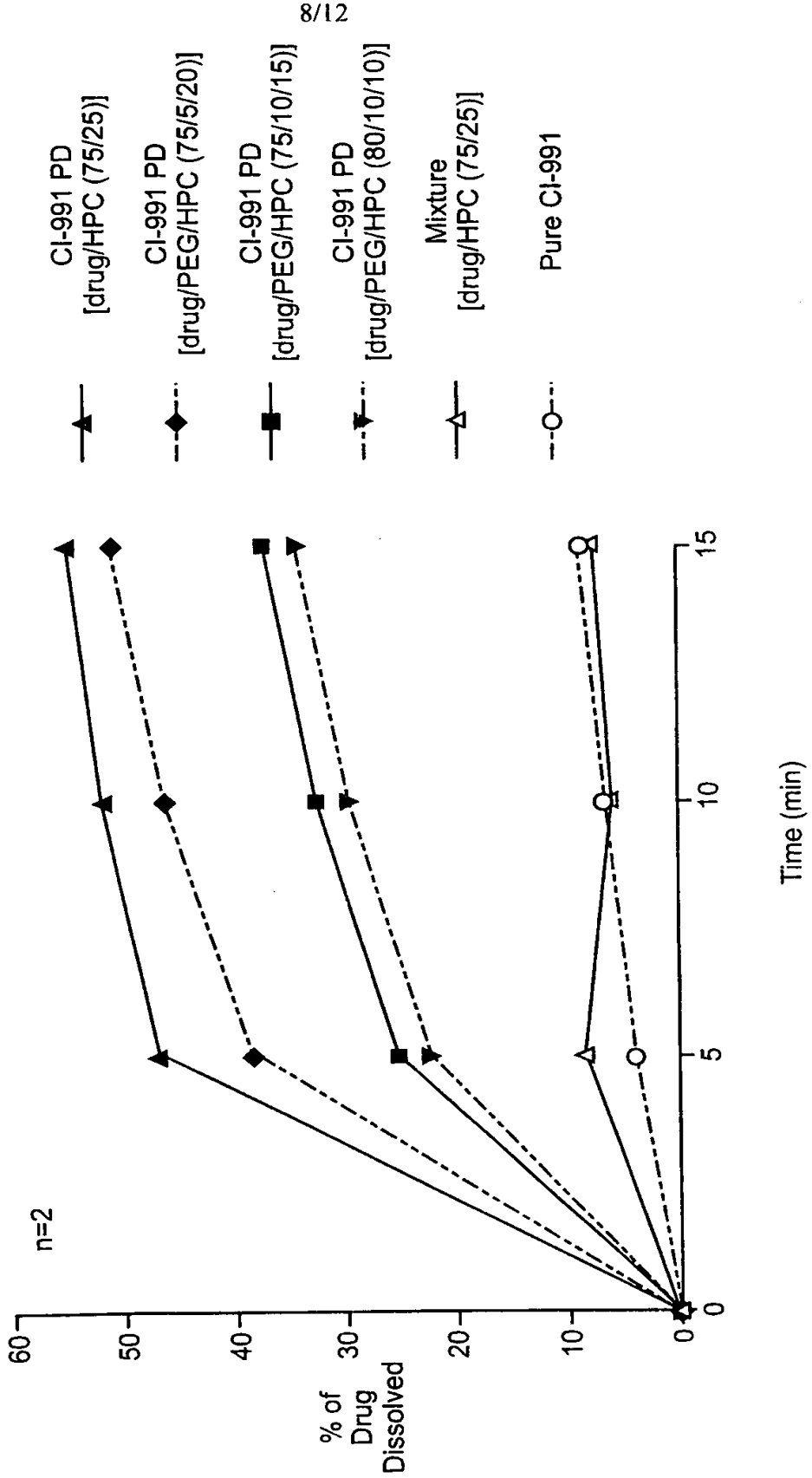

n=2
% of Drug Dissolved
0
10
20
30
40
50
60
0
5
10
15
Time (min)
CI-991 PD [drug/HPC (75/25)]
CI-991 PD [drug/PEG/HPC (75/5/20)]
CI-991 PD [drug/PEG/HPC (75/10/15)]
CI-991 PD [drug/PEG/HPC (80/10/10)]
Mixture [drug/HPC (75/25)]
Pure CI-991

FIG-9

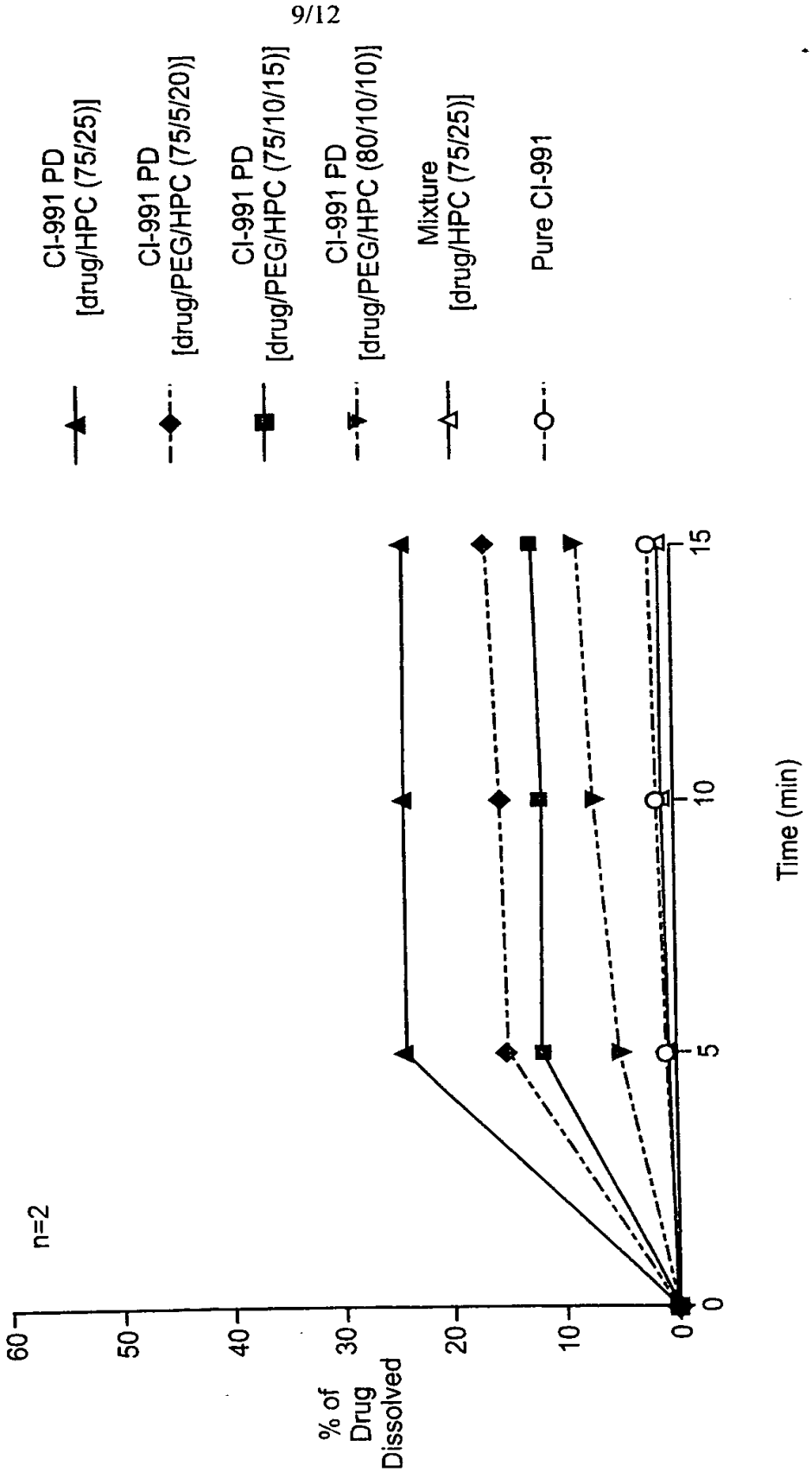
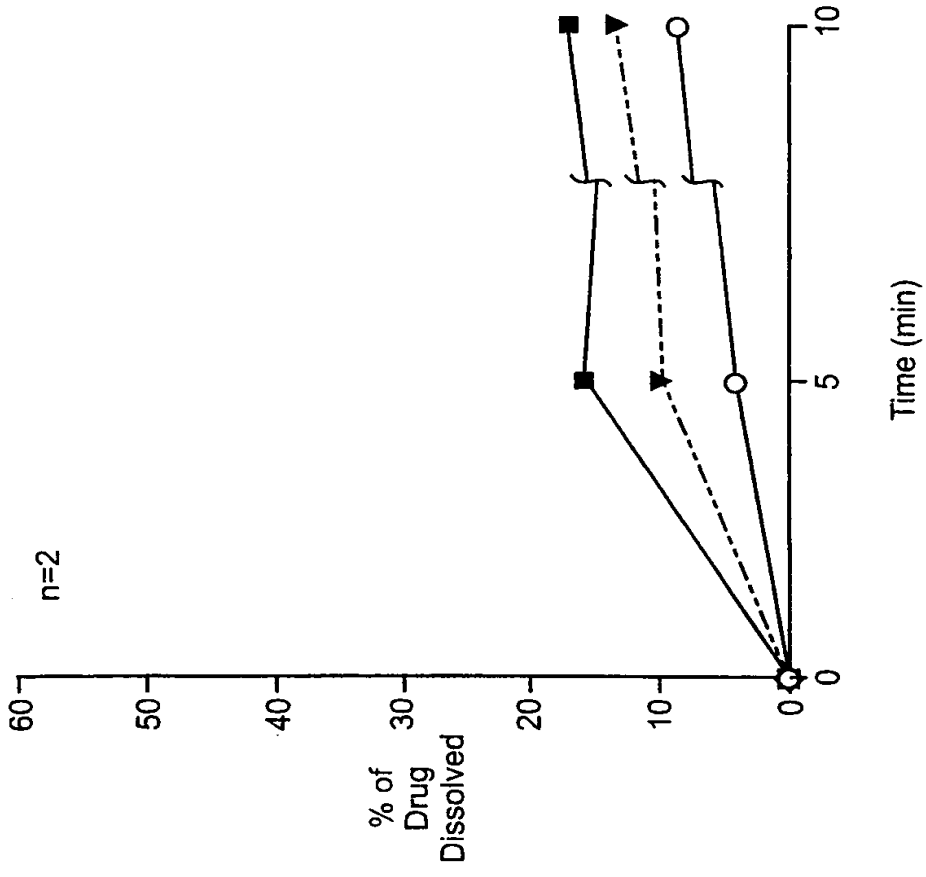

CI-991 PD [drug/HPC (75/25)]
CI-991 PD [drug/PEG/HPC (75/5/20)]
CI-991 PD [drug/PEG/HPC (75/10/15)]
CI-991 PD [drug/PEG/HPC (80/10/10)]
Mixture [drug/HPC (75/25)]
Pure CI-991
n=2
% of Drug Dissolved
60
50
40
30
20
10
0
0
5
10
15
Time (min)

FIG-10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% of Drug Dissolved
60
50
40
30
20
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0
5
10
Time (min)
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CI-991 PD [drug/PEG/PVP (80/10/10)]
Pure CI-991 PD

FIG-11

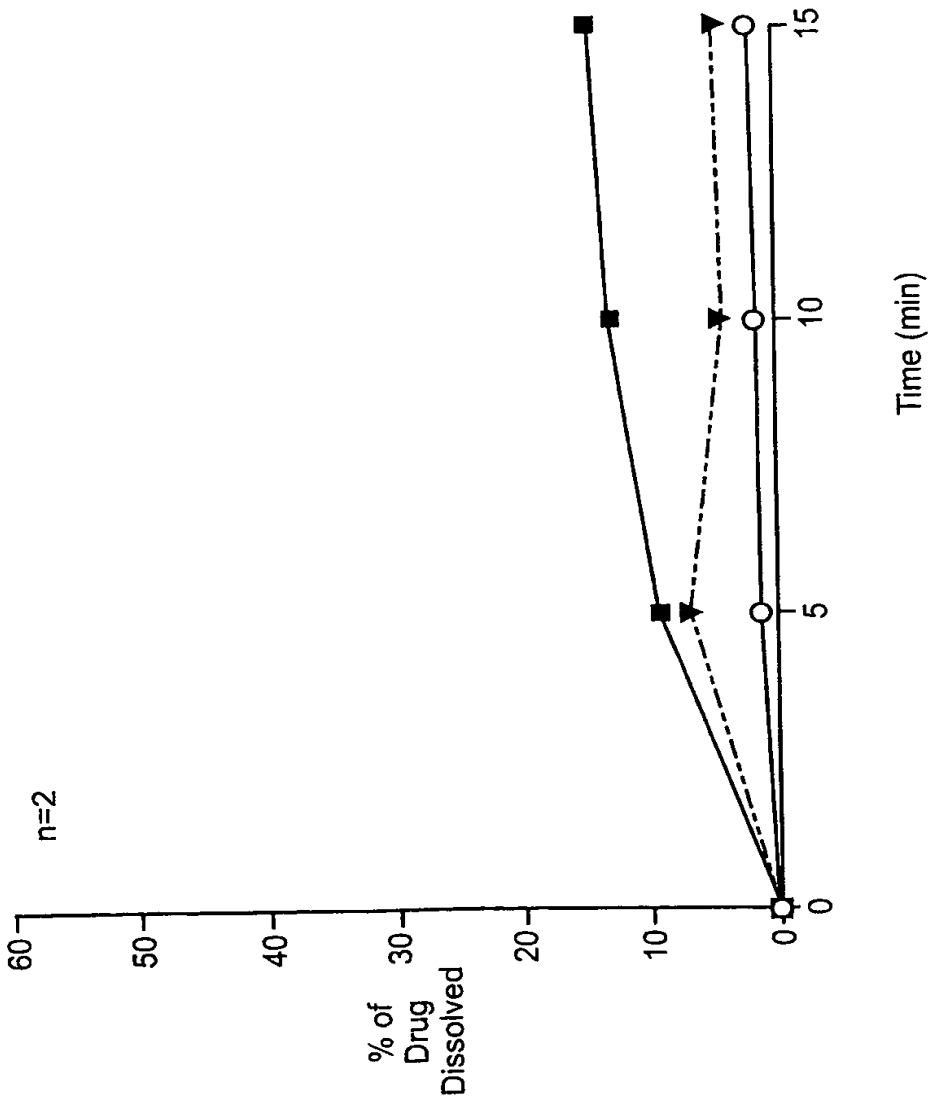
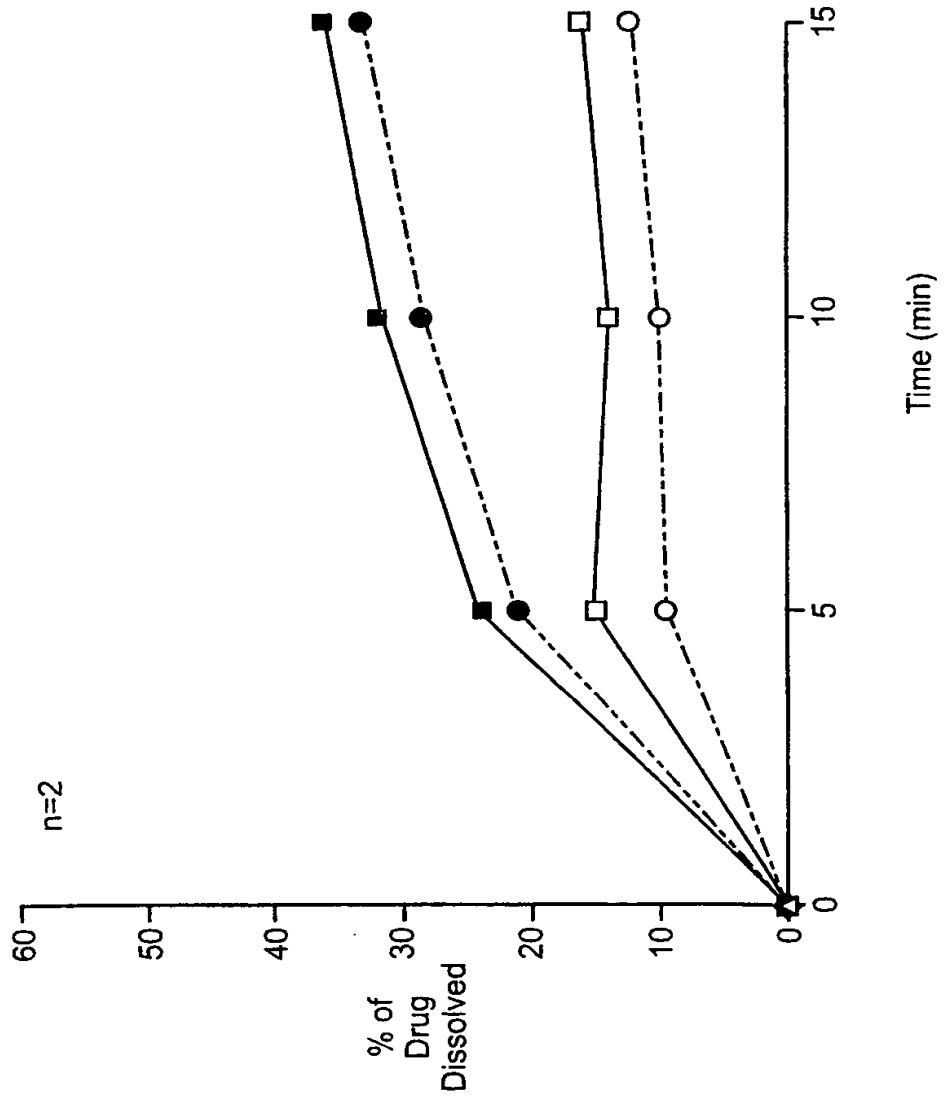

CI-991 PD [drug/PEG/PVP (75/10/15)]
CI-991 PD [drug/PEG/PVP (80/10/10)]
Pure CI-991
n=2
% of Drug Dissolved
0
10
20
30
40
50
60
0
5
10
15
Time (min)

FIG-12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CI-991/PVP PD [drug/PEG/PVP (75/10/15)]
CI-991/PVP PD [drug/PEG/PVP (80/10/10)]
n=2
% of Drug Dissolved
Time (min)
0
10
20
30
40
50
60
0
5
10
15

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/15693

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/14 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 11749 A (WARNER LAMBERT CO) 24 June 1993 see page 8 - page 9; example 1 ---	1-3,7
X	US 5 641 516 A (GRABOWSKI SVEN ET AL) 24 June 1997 see column 4 - column 5; examples 1-7 ---	1,5-7
X	EP 0 740 934 A (BAYER AG) 6 November 1996 see column 5; example 1 see column 6; example 12 see column 7; example 19 ---	1,5-7
X	EP 0 137 198 A (FUJISAWA PHARMACEUTICAL CO) 17 April 1985 see page 2, line 3 - line 15 see page 7; example 3 ---	1,5,6
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1998	09/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/15693

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 552 708 A (FUJISAWA PHARMACEUTICAL CO) 28 July 1993 see page 8; examples 3,5	1,5,6
X	EP 0 580 860 A (NIPPON SHINYAKU CO LTD) 2 February 1994 see page 7; example 4	1
X	CHEMICAL ABSTRACTS, vol. 118, no. 93, 14 June 1919 Columbus, Ohio, US; abstract no. 240956, KENJI N. ET AL: "Solid dispersions containing thiazolidines" XP002085367 see abstract	1-3,7
X	& JP 05 004919 A (JPN KOKAI TOKKYO KOHO) 14 January 1993 see the whole document	1-3,7
X	CHEMICAL ABSTRACTS, vol. 124, no. 96, 18 March 1919 Columbus, Ohio, US; abstract no. 156003, KUSAI A. ET AL: "Solid dispersions of thiazolidine derivative or pharmaceutical preparatin comprising said dispersion" XP002085368 see abstract	1-3,6
X	& WO 95 32713 A (SANKYO CO LTD) see the whole document	1-3,6

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 15693

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are theoretically defined by the expresssions "sparingly water-soluble particulate pharmaceutical agent" and "water-soluble polymer" in Claim 1 the search has been restricted for economic reasons. The search was limited to the general concepts of "sparingly water-soluble particulate pharmaceutical agent" and "water-soluble polymer" and to the compounds cited in the examples and claimed in Claims 31-7 (PCT Search Guidelines PCT/GL2, Chapter III, 2.1., 3.6. and 3.7.).

Some compounds cited in the description as "sparingly water-soluble particulate pharmaceutical agent" don't in fact enter in this solubility category (see for instance "salicylic acid" on page 4, line 22) and some polymers cited as "water-soluble polymer" are not polymers (see tweens or lecithin, on page 5 line 4), leading to an unclarity of claim 1 (Article 6 PCT).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/15693

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311749 A	24-06-1993	AT 157864 T	15-09-1997
		AU 3142693 A	19-07-1993
		DE 69222182 D	16-10-1997
		DE 69222182 T	26-02-1998
		DK 617612 T	14-04-1998
		EP 0617612 A	05-10-1994
		ES 2109377 T	16-01-1998
		GR 3025501 T	27-02-1998
		IL 104179 A	20-11-1997
		JP 7504162 T	11-05-1995
		MX 9207390 A	01-06-1993
		NZ 245483 A	21-12-1995
		PT 101132 A	31-03-1994
		SG 43179 A	17-10-1997
		ZA 9209789 A	23-06-1993
US 5641516 A	24-06-1997	DE 4226753 A	17-02-1994
		AU 4457293 A	17-02-1994
		CA 2103961 A	14-02-1994
		EP 0596203 A	11-05-1994
		JP 6172160 A	21-06-1994
		MX 9304658 A	28-02-1994
		NO 932875 A	14-02-1994
EP 0740934 A	06-11-1996	DE 19515972 A	07-11-1996
		CA 2175293 A	03-11-1996
		JP 8301789 A	19-11-1996
EP 0137198 A	17-04-1985	JP 1723596 C	24-12-1992
		JP 4012245 B	04-03-1992
		JP 60038322 A	27-02-1985
		AT 382779 B	10-04-1987
		AT 251584 A	15-09-1986
		AU 564506 B	13-08-1987
		AU 3130684 A	14-02-1985
		BE 900348 A	11-02-1985
		CA 1228815 A	03-11-1987
		CH 660967 A	30-06-1987
		DK 388884 A,B,	12-02-1985
		FI 843083 A,B	12-02-1985
		FR 2550444 A	15-02-1985
		GB 2145332 A,B	27-03-1985
		GR 80004 A	30-11-1984
		HK 6688 A	29-01-1988
		IE 57757 B	24-03-1993
		US 4654206 A	31-03-1987
EP 0552708 A	28-07-1993	CA 2087932 A	25-07-1993
		JP 5262642 A	12-10-1993
		US 5340591 A	23-08-1994
EP 0580860 A	02-02-1900	DE 69222847 D	27-11-1997
		DE 69222847 T	20-05-1998
		GR 3025864 T	30-04-1998
		US 5456923 A	10-10-1995
		AT 159426 T	15-11-1997
		AU 1537292 A	17-11-1992
		CA 2108575 A	17-10-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/15693

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0580860 A		DK 580860 T	25-05-1998
		ES 2111065 T	01-03-1998
		WO 9218106 A	29-10-1992
		JP 2527107 B	21-08-1996

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
5741-01-CA		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 98/ 15693	29/07/1998	21/08/1997
Applicant		
WARNER-LAMBERT COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established by this Authority to read as follows:

   SOLID PHARMACEUTICAL DOSAGE FORMS IN FORM OF A PARTICULATE DISPERSION

5. With regard to the **abstract,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. 8
   - [ ] as suggested by the applicant.
   - [X] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/ 15693

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are theoretically defined by the expresssions "sparingly water-soluble particulate pharmaceutical agent" and "water-soluble polymer" in Claim 1 the search has been restricted for economic reasons. The search was limited to the general concepts of "sparingly water-soluble particulate pharmaceutical agent" and "water-soluble polymer" and to the compounds cited in the examples and claimed in Claims 31-7 (PCT Search Guidelines PCT/GL2, Chapter III, 2.1., 3.6. and 3.7.).

Some compounds cited in the description as "sparingly water-soluble particulate pharmaceutical agent" don't in fact enter in this solubility category (see for instance "salicylic acid" on page 4, line 22) and some polymers cited as "water-soluble polymer" are not polymers (see tweens or lecithin, on page 5 line 4), leading to an unclarity of claim 1 (Article 6 PCT).

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Solid particulate dispersions of pharmaceutical agents in a matrix of a water-soluble polymer exhibiting good aqueous dissolution and enhanced bioavailability. The method of the invention utilizes water soluble polymers such as polyvinylpyrrolidone, hydroxypropyl cellulose or hydroxypropylmethyl cellulose as carriers. The invention provides for mixing or eyxtracting the active ingredients in solid particulate form with the polymeric carrier at a temperature at which the polymer softens, or even melts, but the drug remains solid or crystalline. The drug particles thus become coated and produce a product that is matrix coated, i.e. a particulate dispersion.

INTERNATIONAL SEARCH REPORT

Internat[redacted] Application No
PCT/[redacted] 98/15693

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/14 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 11749 A (WARNER LAMBERT CO) 24 June 1993 see page 8 - page 9; example 1	1-3,7
X	US 5 641 516 A (GRABOWSKI SVEN ET AL) 24 June 1997 see column 4 - column 5; examples 1-7	1,5-7
X	EP 0 740 934 A (BAYER AG) 6 November 1996 see column 5; example 1 see column 6; example 12 see column 7; example 19	1,5-7
X	EP 0 137 198 A (FUJISAWA PHARMACEUTICAL CO) 17 April 1985 see page 2, line 3 - line 15 see page 7; example 3	1,5,6

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1998	09/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 552 708 A (FUJISAWA PHARMACEUTICAL CO) 28 July 1993 see page 8; examples 3,5	1,5,6
X	EP 0 580 860 A (NIPPON SHINYAKU CO LTD) 2 February 1994 see page 7; example 4	1
X	CHEMICAL ABSTRACTS, vol. 118, no. 93, 14 June 1919 Columbus, Ohio, US; abstract no. 240956, KENJI N. ET AL: "Solid dispersions containing thiazolidines" XP002085367 see abstract	1-3,7
X	& JP 05 004919 A (JPN KOKAI TOKKYO KOHO) 14 January 1993 see the whole document	1-3,7
X	CHEMICAL ABSTRACTS, vol. 124, no. 96, 18 March 1919 Columbus, Ohio, US; abstract no. 156003, KUSAI A. ET AL: "Solid dispersions of thiazolidine derivative or pharmaceutical preparatin comprising said dispersion" XP002085368 see abstract	1-3,6
X	& WO 95 32713 A (SANKYO CO LTD) see the whole document	1-3,6

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/15693

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311749 A	24-06-1993	AT 157864 T	15-09-1997
		AU 3142693 A	19-07-1993
		DE 69222182 D	16-10-1997
		DE 69222182 T	26-02-1998
		DK 617612 T	14-04-1998
		EP 0617612 A	05-10-1994
		ES 2109377 T	16-01-1998
		GR 3025501 T	27-02-1998
		IL 104179 A	20-11-1997
		JP 7504162 T	11-05-1995
		MX 9207390 A	01-06-1993
		NZ 245483 A	21-12-1995
		PT 101132 A	31-03-1994
		SG 43179 A	17-10-1997
		ZA 9209789 A	23-06-1993
US 5641516 A	24-06-1997	DE 4226753 A	17-02-1994
		AU 4457293 A	17-02-1994
		CA 2103961 A	14-02-1994
		EP 0596203 A	11-05-1994
		JP 6172160 A	21-06-1994
		MX 9304658 A	28-02-1994
		NO 932875 A	14-02-1994
EP 0740934 A	06-11-1996	DE 19515972 A	07-11-1996
		CA 2175293 A	03-11-1996
		JP 8301789 A	19-11-1996
EP 0137198 A	17-04-1985	JP 1723596 C	24-12-1992
		JP 4012245 B	04-03-1992
		JP 60038322 A	27-02-1985
		AT 382779 B	10-04-1987
		AT 251584 A	15-09-1986
		AU 564506 B	13-08-1987
		AU 3130684 A	14-02-1985
		BE 900348 A	11-02-1985
		CA 1228815 A	03-11-1987
		CH 660967 A	30-06-1987
		DK 388884 A,B,	12-02-1985
		FI 843083 A,B	12-02-1985
		FR 2550444 A	15-02-1985
		GB 2145332 A,B	27-03-1985
		GR 80004 A	30-11-1984
		HK 6688 A	29-01-1988
		IE 57757 B	24-03-1993
		US 4654206 A	31-03-1987
EP 0552708 A	28-07-1993	CA 2087932 A	25-07-1993
		JP 5262642 A	12-10-1993
		US 5340591 A	23-08-1994
EP 0580860 A	02-02-1900	DE 69222847 D	27-11-1997
		DE 69222847 T	20-05-1998
		GR 3025864 T	30-04-1998
		US 5456923 A	10-10-1995
		AT 159426 T	15-11-1997
		AU 1537292 A	17-11-1992
		CA 2108575 A	17-10-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[redacted] 98/15693

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0580860 A		DK 580860 T	25-05-1998
		ES 2111065 T	01-03-1998
		WO 9218106 A	29-10-1992
		JP 2527107 B	21-08-1996

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 29 March 1999 (29.03.99)	
International application No. PCT/US98/15693	**Applicant's or agent's file reference** 5741-01-CA
International filing date (day/month/year) 29 July 1998 (29.07.98)	**Priority date** (day/month/year) 21 August 1997 (21.08.97)
Applicant GHEBRE-SELLASSIE, Isaac	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

16 February 1999 (16.02.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Maria Victoria CORTIELLO

Telephone No.: (41-22) 338.83.38

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A82-1000-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/AT97/00234	International filing date (*day/month/year*) 04 November 1997 (04.11.1997)	Priority date (*day/month/year*) 04 November 1996 (04.11.1996)
International Patent Classification (IPC) or national classification and IPC B26B 13/24		
Applicant ADAM, Herbert		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 April 1998 (07.04.1998)	07 September 1998 (07.09.1998)
Name and mailing address of the IPEA/EP European Patent Office D-80298 Munich, Germany Facsimile No. 49-89-2399-4465	Authorized officer Telephone No. 49-89-2399-0

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AT97/00234

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 2-5, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages 1, filed with the letter of 18 August 1998 (18.08.1998).

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 5(in part), 6-18, filed with the letter of 03 April 1998 (03.04.1998),
Nos. 1-4,5(in part), filed with the letter of 18 August 1998 (18.08.1998).

☒ the drawings, sheets/fig 1/3-3/3, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-18	YES
	Claims		NO
Inventive step (IS)	Claims	1-18	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-18	YES
	Claims		NO

2. Citations and explanations

GB-A-1 537 614 is regarded as the closest prior art and discloses double scissors, in particular for cutting hair, with two pairs of scissors arranged essentially parallel at a distance from each other and each having two blades, the pairs of blades being different; the scissors can be actuated at the same time, only one of the two scissors having finger rings and the end of the leg of the other pair of scissors being coupled with the leg of the scissors with the finger rings and wherein the two blades of each pair of scissors are pivotably connected to each other via a connecting element that can be adjusted independently of the connecting element of the other pair of scissors.

The subject matter of the independent claim differs therefrom in that the connecting elements are coupled together by a hinge pin, that the hinge pin is fitted securely in one of the connecting elements and engages in an axial hole in the other connecting element, and that the legs of one of the pairs of scissors are connected to the legs of the other pair of scissors in the areas between the connecting elements and the points at which the legs of the

scissors are coupled to each other.

The combination of these differentiating features ensures that, given the three connecting points, the middle one of which is secure and the other two of which are axial, that is can move in the direction of the connection, the distance and the angle between the scissors can be adjusted more easily.

Documents AT-B-395 552 and DE-A-27 32 535 describe double scissors with only two connecting points.